REMARKS

The Specification has been amended to correct two typographical errors. Claim 1 has been amended to recite that the amount of naloxone is from 5 to 50 mg. and the amount of oxycodone is from 10 to 100 mg, in order to align the amounts with the recited 2:1 ratio.

The Examiner's statement regarding a lack of English translations of the German priority documents is duly noted. Applicants are obtaining English translations, and will provide them to the Examiner upon receipt thereof.

Claims 45 and 47-58 of the instant application stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 7-8, 11-17, 43-46 and 48-49 of copending Application No. 10/510,673. Since none of the pending claims 45-58 of the instant application, nor any of the pending claims of copending Application No. 10/510,673 has been patented, Applicants respectfully request that the Examiner hold in abeyance this provisional obviousness-type double patenting rejection until such time when these claims are in final form and otherwise in condition for allowance, and the claims of Application No. 10/510,673 over which double patenting is alleged are allowed. Until such time, there is no double patenting and no way to determine double patenting. MPEP § 804.01.I(B)(1).

The Examiner has rejected claims 45-58 under 35 U.S.C. § 103(a) as being unpatentable over Kaiko et al. (WO 99/32119) in view of Pachter et al. (U.S. Patent No. 3,773,955). Applicants respectfully traverse.

The presently claimed invention comprises a controlled release dosage form containing oxycodone and naloxone in a 2:1 weight ratio. It is respectfully submitted that the Examiner's proposed combination of the Kaiko and Pachter references as a basis for an obviousness rejection of the present claims was arrived at through an impermissible hindsight reconstruction of the present claims without regard to the disparate teachings of the cited references.

The present invention is directed to providing a controlled release opioid formulation which provides efficient analgesia and at the same time shows a reduced side effect profile. Furthermore, it is anticipated that the formulation should have the advantage of being less prone to abuse (*see, e.g.,* page 9, lines 13 to 24).

These objectives are attained by the subject matter of independent claim 45, *i.e.*, a controlled release formulation comprising oxycodone and naloxone in a 2:1 ratio in a controlled release matrix and with oxycodone and naloxone being present in the specific amounts indicated. Attached hereto as Exhibit A is a copy of Clinical Study Results for Controlled Release Oxycodone/Naloxone Formulations performed regarding, *inter alia*, formulations which are within the scope of the claimed inventions. ("Clinical Study Report"). The efficacy of the presently claimed formulations is apparent from the attached Clinical Study Report, which analyzed the effect of controlled release formulations as described in the present application for different ratios of oxycodone/naloxone on factors such as reduction of pain intensity, improvement of bowel function index, occurrence of adverse effects, avoidance of diarrhea, and tolerability and preference by patients. The outcome of the study clearly shows that an optimal balance between these various factors can be achieved with controlled release oxycodone formulations as presently claimed which comprise the actives in a 2:1 ratio as recited in independent claim 45. The following publications, which also discuss the efficacy of the presently claimed invention, are attached hereto as well: Vondrackova et al., Analgesic Efficacy and Safety of Oxycodone in Combination with Naloxone as Prolonged Release Tablets in Patients with Moderate to Severe Chronic Pain, J. Pain, Dec. 2008, 9(12):1144-1154 (Exhibit B); Nadstawek et al., Patients Assessment of a Novel Therapeutic Approach for the Treatment of Severe, Chronic Pain, Int. J. Clin. Pract. 2008, 62(8):1159-1167 (Exhibit C); and Meissner et al., A Randomised Controlled Trial With Prolonged-Release Oral Oxycodone and Naloxone to Prevent and Reverse Opioid-Induced Constipation, Eur. J. Pain (2008) doi:10.1016/j.ejpain2008.06.012 (article in press; Exhibit D).

Thus, the objective of the present application is to provide a controlled release opioid formulation which ensures effective analgesia and at the same time reduces side effects and is less prone to abuse than formulations known from the art. From what has been stated above, it is clear that the controlled release formulations as covered by independent claim 45 beneficially address these various objectives.

The Kaiko prior art reference discloses formulations of an oral dosage form of opioid analgesics which are "subject to less abuse potential via the oral route than prior commercially available dosage forms" (page 6, lines 10-12). Kaiko states that its formulations are analgesically effective when administered orally at the prescribed dose, but which provides a negative, aversive experience if administered to a physically dependent

subject orally at more than the prescribed dose, *e.g.*, about 2-3 times the usually prescribed dose (page 6, lines 13-16 and 27-30). Kaiko also states that the disclosed dosage forms are not as positively reinforcing in non-physically dependent subjects taking more than the usually prescribed dose, *e.g.*, about 2-3 times the usually prescribed dose of the opioid, as compared to the same amount of the opioid without the antagonist (page 6, lines 17-21). Kaiko acknowledges that, in some embodiments, when orally taken at the prescribed dose, the amount of opioid antagonist included in the dosage form may decrease analgesia somewhat and that the decrease of analgesia may be clinically significant (page 7, lines 8-10, 24-25, 33-34; page 8, lines 28-34; page 9, lines 12-13).

While Kaiko discloses that naloxone may be used as the antagonist, no specific amounts or ratios of naloxone are disclosed for the invention. Rather, the only antagonist for which Kaiko discloses specific amount or ratios is naltrexone. In fact, Kaiko contrasts the oral potency of naloxone and naltrexone, stating that naloxone "is absorbed after oral administration, but has been reported to be metabolized into an inactive form in its first passage through the liver such that it has been reported to be only one fiftieth as potent when parenterally administered" (emphasis added), whereas naltrexone, and cyclazocine, "retain much of their efficacy by the oral route" (page 13, lines 27-30 and 32-34).

Kaiko discloses and claims a weight ratio of naltrexone:oxycodone of 0.037 to 0.296:1, and a more preferred ratio of 0.056 to 0.222:1. If one multiplies these ratios by a factor of 50 to account for the stated poor oral potency of naloxone as compared to naltrexone, the ratio of naloxone:oxycodone would be 1.85 to 14.8:1, and the more preferred range would be 2.8 to 11.1:1. Thus, in contrast to the presently claimed oxycodone:naloxone ratio of 2:1, Kaiko suggests that the ratio may be about 2:3.7 or higher.

The Examiner states that "Kaiko et al. teach that oxycodone-naloxone composition[s] can have [a] ratio of 2.5-5:1 parts by weight" (Office Action, page 6, last 2 lines), however that statement is Kaiko's description of prior art U.S. Patent No. 4,457,933 to Gordon and Pachter. It is submitted that a statement describing the prior art can not be said to be a teaching by Kaiko to use the prior art weight ratios.

The Examiner agrees that "Kaiko et al. does not teach a pharmaceutical preparation containing oxycodone:naloxone with the specific weight ratio of 2:1 or a preparation in the form of specific pharmaceutically acceptable and equally active free base salts" (Office Action, page 7, paragraph 2). The Examiner relies on Pachter to allegedly teach the use of a

weight ratio of 2:1 in the controlled release oral dosage form disclosed in Kaiko. Applicants respectfully disagree with the proposed combination of references for the following reasons.

Notably, Kaiko cites to and distinguishes Pachter, stating that Pachter described compositions to "prevent parenteral abuse of the analgesic agents" and "was not concerned with oral abuse of opioids" (Kaiko, page 5, lines 10-14). In contrast, as described above, Kaiko was concerned with oral dosage forms which can prevent abuse if taken at more than the prescribed dose orally.

Pachter clearly teaches immediate release formulations of oxycodone and naloxone only, such as, *e.g.*, solutions and liquids comprising these active agents. The teaching of Pachter is that dosages of oxycodone and naloxone such as 2-20:1 can be used to obtain immediate release formulations which upon oral administration provide analgesic efficacy while upon parenteral administration lead to precipitated withdrawal effects in physically dependent subjects. Thus, Pachter et al. is concerned with dosage forms that upon oral administration provide efficient analgesia but which prevent parenteral abuse.

A person skilled in the art at the priority date of the present application would have had no motivation to combine Kaiko and Pachter as these two prior art references clearly aim at different objectives, Kaiko being concerned with dosage forms that are less abuse-prone upon oral administration while Pachter was concerned with immediate release formulations that are less prone to parenteral abuse. There would simply have been no reason for a skilled person to combine two references which aim at different objectives.

Further, in view of the teaching of Kaiko that orally administered naloxone "has been reported to be only one fiftieth as potent as when parenterally administered" (Kaiko, page 13, lines 27-30), even if one were to combine Kaiko and Pachter, the 2-20:1 oxycodone:naloxone ratio disclosed in Pachter to prevent parenteral abuse would have been converted to about 2-20:50 in order to prevent oral abuse.

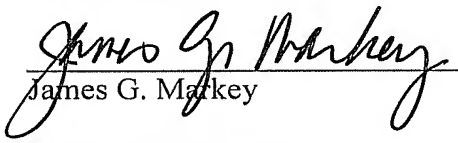
Furthermore, present independent claim 45 is directed to controlled release dosage forms comprising oxycodone and naloxone in a controlled release matrix in a 2:1 ratio with the indicated specific amounts. The data mentioned in the clinical study and the statements in the application as filed clearly point out that such controlled release formulation are efficient in providing analgesia and improving the side effect profile while also being less prone to parenteral abuse.

However, there is no indication in Kaiko or in Pachter that providing oxycodone and naloxone in a 2:1 ratio with the indicated amounts specified in a controlled release matrix would allow achievement of this aggregation of beneficial characteristics, *i.e.*, analgesic efficacy, improved side effect profile and reduced oral abuse potential. In view of the beneficial characteristics of the presently claimed formulations and in view of the fact that none of the prior art references teaches that these combined effects could be achieved by selecting a specific ratio for these two active agents and putting the two active agents in the specific ratio in a controlled release matrix, we respectfully submit that the claimed subject matter is inventive over the prior art, and request withdrawal of the rejection under 35 U.S.C. § 103(a).

No fee is believed to be due for this response, beyond the three month extension provided for in accompanying documents. However, should any additional fee be required, please charge such fee to Duane Morris Deposit Account No. 04-1679.

Respectfully submitted,

Date: January 21, 2009



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